IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	H. William BOSCH et al.
Title:	LIQUID DOSAGE COMPOSITIONS OF STABLE NANOPARTICULATE ACTIVE AGENTS
Appl. No.:	10/619,539
Filing Date:	7/16/2003
Examiner:	Susan T. Tran
Art Unit:	1615
Confirmation Number:	6324

REPLY BRIEF

Mail Stop Appeal Brief - Patents
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Sir:

Under the provisions of 37 C.F.R. § 41.39, this Reply Brief is submitted in response to the Examiner's Answer, dated April 27, 2010. Although Appellants believe that no fee is required, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

REAL PARTY IN INTEREST

The real party in interest in this appeal is Elan Pharma International, Ltd., which is the assignee of the present application as recorded at Reel/Frame numbers 015072/0837.

RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

STATUS OF CLAIMS

Claims 4, 36, 38, 40, 42, 53 and 83 are canceled.

Claims 1-3, 5-35, 37, 39, 41, 43-52, 54-82, 84-123 are pending in the application, with claims 46-52, 54-82, 84-123 withdrawn from consideration. The claims under examination and the withdrawn claims are related as product and process claims. Therefore, the withdrawn process claims are subject to a rejoinder upon allowance of the corresponding product claims.

Claims 1-3, 5-35, 37, 39, 41, 43-45 are finally rejected, and are the subject of this appeal. The pending claims are presented in Appendix A of this Reply Brief.

STATUS OF AMENDMENTS

No claim amendments were made in the response to final Office Action, filed on December 18, 2008. In the final Office Action dated October 8, 2008, the Examiner indicated entry and consideration of an amendment filed July 3, 2008. No other amendments or submissions are pending in the application.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is to be argued in the brief. The citation to the specification is shown in the parenthesis.

Independent claim 1 reads as follows:

1. A stable nanoparticulate liquid dosage composition **{p. 8, ll. 2-3, 24-25}** comprising:

(a) particles of at least one active agent having an effective average particle size of less than 2000 nm **{p. 8, ll. 3-4, 25-26; p. 30, ll. 5-7}**;

(b) at least one surface stabilizer **{p. 8, ll. 4, 26-27}**;

(c) at least one osmotically active crystal growth inhibitor **{p. 8, ll. 5, 27-28}** that is capable of preventing crystal growth of the active agent **{p. 28, ll. 15-17}** at ambient temperature **{p. 28, ll. 18-19}**, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol **{p. 8, l. 7; p. 28, l. 18}**, propylene glycol **{p. 28, ll. 18-19}**, mannitol **{p. 8, l. 7; p. 28, l. 19}**, sucrose **{p. 28, l. 20}**, glucose **{p. 28, l. 20}**, fructose **{p. 28, l. 20}**, mannose **{p. 28, l. 20}**, lactose **{p. 28, l. 20}**, xylitol **{p. 28, l. 20}**, sorbitol **{p. 28, l. 20}**, trehalose **{p. 28, l. 20}**, a polysaccharide **{p. 28, l. 21}**, a mono-polysaccharide **{p. 28, l. 21}**, a di-polysaccharides **{p. 28, l. 21}**, a sugars **{p. 28, l. 21}**, a sugar alcohol **{p. 28, l. 21}**, sodium chloride **{p. 8, l. 7; p. 28, l. 22}**, potassium chloride **{p. 28, l. 22}**, magnesium chloride **{p. 28, l. 22}**, and an ionic salt **{p. 28, ll. 22-23}**; and

(d) a liquid media **{p. 8, l. 30}**,

wherein the liquid dosage composition does not incorporate a cloud point modifier **{p. 6, ll. 7-24; p. 7, ll. 24-29; p. 9, ll. 8-9}**.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The first rejection to be reviewed on appeal is the rejection of claim 2 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement.

The second rejection to be reviewed on appeal is the rejection of claim 15 under 35 U.S.C. § 112, second paragraph, for allegedly failing to further limit the subject matter of claim 1.

The third rejection to be reviewed on appeal is the rejection of claims 1-3, 5, 6, 8-19, 21-24, 27-29, 32-35, 37, 39, 41 and 43-45 under 35 U.S.C. § 102(b) for alleged anticipation by U.S. Patent No. 5,302,401 to Liversidge et al. ("Liversidge '401").

The fourth rejection to be reviewed on appeal is the rejection of claims 1-3, 5-24, 26-31, 35, 37, 39, 41 and 43-45 under 35 U.S.C. § 102(e) for alleged anticipation by U.S. Patent Application No. 2003/0077329 by Kipp et al. ("Kipp").

The fifth rejection to be reviewed on appeal is the rejection of claims 1-3, 5-24, 27-29, 32-35, 37, 39, 41 and 43-45 under 35 U.S.C. § 103(a) over Liversidge '401, in view of PCT Application Publication No. WO 01/78505 by Brockbank et al. ("Brockbank") or Kipp.

The sixth rejection to be reviewed on appeal is the rejection of claims 25-35, 37, 39, 41 and 43-45 under 35 U.S.C. § 103(a) over Liversidge '401, in view of U.S. Patent Application Publication No. 2005/0004049 by Liversidge ("Liversidge '049").

ARGUMENT

Pursuant to 37 C.F.R. §41.39, Appellants take this opportunity to respond to certain comments made in the Examiner's Answer dated April 27, 2010 ("the Answer").

I. Liversidge '401

A. Contrary to the Examiner's contention, Liversidge '401 fails to teach a stable liquid dosage composition.

In response to Appellants' argument that "unlike the claimed liquid dosage composition, the nanoparticulate active agent composition of Liversidge '401 is in lyophilized dry powder form," the Examiner asserts that "Liversidge '401 does teach a liquid dosage form as claimed" because the reference allegedly discloses that "a liquid formulation is obtained that comprises nanoparticles of therapeutic or diagnostic suspended in a solution of cryoprotectant." The Answer, page 11, 1st full paragraph.

For the ease of discussion, the relevant passages of Liversidge '401 are excerpted below:

> *This invention further discloses a method of making nanoparticles having a surface modifier adsorbed on the surface and a cryoprotectant associated therewith, comprised of contacting said nanoparticles with the cryoprotectant for a time and under conditions sufficient to form a nanoparticle-cryoprotectant composition.* ***That composition allows the nanoparticles to be lyophilized.***
>
> *This method involves the preparation of therapeutic or diagnostic nanoparticles, as discussed elsewhere herein, and contacting those nanoparticles with a cryoprotectant. Contacting may be by admixing a suspension of nanoparticles with a solution of cryoprotectant,* ***followed by lyophilization at a temperature and for a time sufficient to effect freeze-drying of the nanoparticle suspension****.*

Liversidge '401, column 5, line 56, through column 6, line 2; emphasis added.

Accordingly, one of ordinary skill in the art would have understood that the mixture of a suspension of drug nanoparticles and a solution of cryoprotectant is only an intermediate product

rather than a final product. This intermediate product is further processed by a lyophilization step to obtain the dry powder. As such, there is no recognized stability problem associated with the intermediate mixture. Indeed, if the intermediate liquid form were meant to be the final product, there would have had been no reason to add the cryoprotectant because a cryoprotectant is only added to facilitate the lyophilization process. The Examiner can only make her conclusion by taking a snap shot of a certain time point of the prior-art process, a time point that is itself illogical in the process of Liversidge '401, rather than interpreting the prior-art teaching ***as a whole***, as required by MPEP 2141.02.

Similarly, the Examiner also alludes to Liversidge '401's teaching of reconstitution of the lyophilized powder into a liquid formulation as anticipating the claimed invention. Again, it is unclear from the teachings of Liversidge '401 how one of ordinary skill in the art identifies a cryoprotectant and makes the leap to a crystal growth modifier without the aid of the Appellants' claimed invention.

Moreover, the prior art relied on in an anticipation rejection "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net Moneyin Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1369 (2008). Accordingly, it is insufficient to support an anticipation rejection by merely pointing out certain claim elements in the cited reference. The Examiner is required to articulate how the elements are "arranged as in the claim."

Finally, there is no discussion in Liversidge '401 about the stability of the reconstituted lyophilized composition. For a reference to be anticipatory, it must be enabling. "The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." MPEP 2121.01 citing *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (2003). Having no discussion of stability or the need to reduce growth of the nanoparticulate crystals, Liversidge '401 is insufficient to teach one

of ordinary skill in the art how to make and use Appellants' claimed invention, which requires a stable nanoparticulate liquid dosage at ambient temperature.

B. The cryoprotectant of Liversidge '401 fails to teach or suggest the osmotically active crystal growth inhibitor of Appellants' claimed invention.

The Examiner asserts that the cryoprotectant of Liversidge '401 is art recognized equivalent to the osmotically active crystal growth inhibitor of the claimed invention. *See* the Answer, page 6, 2nd full paragraph. Appellants respectfully disagree because the rejection lacks explicit findings as to what a person of ordinary skill would have known about the cryoprotectants in Liversidge '401 and as to whether the cryoprotectants would be suitable as osmotically active crystal growth inhibitors.

Liversidge '401 explicitly defines the cryoprotectant as follows:

> *Cryoprotectans (cryoprotective agents or compounds) are agents that protect chemical compounds, cells, or tissues from the deleterious effects of freezing that may accompany lyophilization. In the case of nanoparticles, cryoprotectants protect from the agglomeration caused by the process of lyophilization, namely freeze-drying.*

Column 5, lines 20-26. In contrast, an osmotically active crystal growth inhibitor of the claimed invention serves to prevent crystal growth of the active agent at ambient temperature, as prescribed by claim 1. In other words, one skilled in the art reading Liversidge '401 would understand that cryoprotectants keep the drug particles from clumping together ***during lyophillization [a freeze-drying process]***; whereas as defined in the specification of the present application, crystal growth inhibitors prevent individual drug particles from individually increasing in crystal size ***at ambient temperature***. There is no teaching or suggestion in Liversidge '401 which would have led one of ordinary skill to select a cryoprotectant to prevent crystal growth at ambient temperature.

Even if, for argument sake, a person of ordinary skill in the art would use the cryoprotectants as crystal growth modifiers, Liversidge '401 is unclear about which cryoprotectant to use. As pointed out by the Examiner, Liversidge '401 lists suitable cryoprotectants as saccharide sucrose, mannitol, Tweens, glycerol and dimethylsulfoxide. *See* column 5, lines 27-33. Liversidge '401, however, contradicts itself in terms of the disclosed cryoprotectants.

Example 3 demonstrates that only with the addition of sucrose did the danazol/PVP solution accomplish what the other excipients could not (the other excipients being Tween and mannitol). *See* column 7, lines 1-17. That is, Tween and mannitol, which were identified to be suitable cryoprotectant, failed to prevent the particles from aggregating during lyophilization. Thus, from the acceptable list of cryoprotectants at column 5, lines 27-33, Example 3 teaches that mannitol and Tweens are not suitable cryoprotectants. Example 4 reemphasizes this point. *See* column 7. Emphatically then, one of ordinary skill would not consider mannitol or Tween suitable cryoprotectants, let alone suitable crystal growth modifiers. This contradiction calls into question the functionality of glycerol and dimethylsulfoxide as cryoprotectants. Because of the discrepancy between the general disclosure of Liversidge '401 and the working examples regarding mannitol and Tween, there is a reason to cast some doubt that glycerol and dimethylsulfoxide would be suitable cryoprotectants, let alone suitable crystal growth modifiers at room temperature as claimed in the present invention.

Accordingly, the rejection rationale, based upon the erroneous conclusion that cryoprotectatns are art recognized equivalents to osmotically active crystal growth inhibitors, is also faulty. The rationale is based upon the mere overlap of compounds in each category of a cryoprotectant and a crystal growth inhibitors. The Examiner's equation of a cryoprotectant with a crystal growth inhibitor lacks any factual support in the cited reference. "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (1989). Indeed, such is not the case with the present

rejection. It is only with the knowledge of Appellants' claimed invention, which expressly recites certain compounds as crystal growth modifiers, can the Examiner equate the cryoprotectants of Liversidge '401 to the claimed crystal growth modifiers of Appellants' claimed invention.

C. The Examiner's certain arguments are irrelevant to the claimed invention.

The Examiner asserts that "the rejected claims do not preclude the liquid formulation to be lyophilized solely for storage purpose." The Answer, page 11, 1st full paragraph. What the claims fails to exclude is irrelevant to whether the references meet each and every limitation of the positively cited limitations of the claims.

Although Appellants' claims do not preclude lyophilization for storage, the claims clearly recite a liquid dosage composition which is stable at ambient temperature, stable meaning maintaining an effective average particle size of less than 2000 nm. The fact that the claims do not recite or exclude certain elements does not support reading such elements into the claims during examination. Therefore, the Examiner is not allowed to read any absent limitations into the claims to bridge the gap between the claims and the cited reference, thereby to arrive at the rejection rationale.

II. Kipp

A. The frozen aqueous matrix of Kipp fails to teach the claimed invention.

The Examiner contends that "the present claims do not preclude storing the liquid composition in the frozen state to prolong the storage stability of the composition," and that "the 'frozen" step is an added benefit to further improve the storage stability." The Answer, at page 12, 1st full paragraph.

Kipp explicitly addressed the instability issue: "We have discovered that freezing may circumvent these instability mechanisms by encasing the drug particles in a frozen aqueous matrix" (page 4, paragraph [0039]). In other words, Kipp acknowledges the stability issue of an aqueous nanoparticle suspension at ambient temperature. Kipp then solves the stability problem by ***freezing*** the composition. As shown in the working examples, Kipp's compositions are stored frozen at -20°C or -70°C. This teaching directly contravenes the claim recitation of a stable nanoparticulate liquid dosage composition comprising, *inter alia*, at least one osmotically active crystal growth inhibitor that is capable of preventing crystal growth of the active agent ***at ambient temperature***.

For this reason alone, Kipp fails to teach each and every aspect to anticipate the claimed invention.

B. Kipp does not teach the osmotically active crystal growth inhibitor of the claimed invention.

It is unclear which compound the Examiner deems to teach the osmotically active crystal growth inhibitor of the claimed invention because the Examiner simply cites to paragraph [0070] identifying crystal growth modifiers, paragraph [0071] identifying cryoprotectants, and paragraph [0073] identifying osmotic agents, absent any elaboration on how any of these compounds teaches the claimed crystal growth inhibitor.

First, the fact that Kipp separately lists each of osmotic agents, cryoprotectants, and crystal growth modifiers is recognition in the art that they are not interchangeable. In other words, in view of Kipp, one of ordinary skill in the art would not consider a cryoprotectant to be an osmotic agent as well as a crystal growth modifier. This conclusion is further supported by Kipp's description of the function of a crystal growth modifier and a cryoprotectant. Specifically, a crystal growth modifier hinders growth or enlargement of the microcrystalline precipitate. *See* paragraph [0070]. A cryoprotectant inhibits agglomeration during the lyophilization process. *See* paragraph [0071]. Notably, this paragraph cites to Liversidge '401,

which is discussed in the foregoing paragraphs. Thus, one of ordinary skill in the art reading Kipp would have concluded that a cryoprotectant, a crystal growth modifier, and an osmotic agent are not art recognized equivalents.

Second, Kipp fails to expressly disclose any of the crystal growth modifiers required by the present claims. *See* paragraph [0070] discussing crystal growth modifiers. Rather, this paragraph incorporates by reference of other patents. The Examiner has not shown whether these incorporated patents fairly teach or suggest the materials now claimed are crystal growth modifiers because they disclose different types of crystal growth modifiers, some of which are required to share structural similarity with the drug.

III. Rationale of Combining Cited References

In the Appeal Brief, Appellants submitted that either there is no reason to combine the teaching of the primary reference with that of the secondary reference or the teaching of the secondary reference fails to compensate the deficiencies of the primary references.

In the Answer, the Examiner simply states that "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference" (the Answer, page 13, 1st full paragraph; and page 14, 1st paragraph).

First, the Examiner's rebuttal does not address Appellants' arguments that the primary references lack the teachings of the crystal growth inhibitor and prevention of crystal growth at ambient temperature. Second, to substantiate an obviousness rejection, the Examiner cannot rely on improper hindsight. In this case, the Examiner cites certain elements of the secondary references, refusing to put such elements in context. By this approach, the Examiner can only make the rejection by extracting claim elements from the prior art, out of context, and then reassembling them with the aid of impermissible hindsight and the teachings of Appellants' claimed invention.

Finally, the Examiner's reply that "Brockbank and Kipp are cited solely for the teaching of cryoprotectant that includes sodium chloride" (the Answer, page 13, 1st full paragraph) fails for the same reasons as discussed *supra*. This is because Appellants' rebuttal refutes the Examiner's faulty premise that one of ordinary skill in the art would consider a cryoprotectant to be an art recognized equivalent to a crystal growth inhibitor, which is addressed above. Brockbank discloses a cryoprotectant "that effectively protects cells during cryopreservation and achieves increased cell viability upon warming from a frozen state." Paragraph [0008]. Brockbank fails to teach that cryoprotectants function to prevent crystal growth in a nanoparticulate suspension at ambient temperature. Accordingly, there is no reason for one of ordinary skill to use the cryoprotectants of Brockbank's composition to prevent crystal growth in view of Brockbank's teaching.

CONCLUSION

Appellants respectfully submit that all pending claims are in condition for allowance, and respectfully request that the rejections be reversed in whole, and that the claims be allowed to issue.

Respectfully submitted,

Date: June 25, 2010

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APPENDIX A: CLAIMS INVOLVED IN APPEAL

1. (Previously Presented) A stable nanoparticulate liquid dosage composition comprising:

(a) particles of at least one active agent having an effective average particle size of less than 2000 nm;

(b) at least one surface stabilizer;

(c) at least one osmotically active crystal growth inhibitor that is capable of preventing crystal growth of the active agent at ambient temperature, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt; and

(d) a liquid media,

wherein the liquid dosage composition does not incorporate a cloud point modifier.

2. (Original) The composition of claim 1, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

3. (Original) The composition of claim 1, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

4. (Cancelled)

5. (Previously Presented) The composition of claim 1, wherein the crystal growth inhibitor is glycerol.

6. (Previously Presented) The composition of claim 1, where the crystal growth inhibitor is mannitol.

7. (Previously Presented) The composition of claim 1, where the crystal growth inhibitor is sodium chloride.

8. (Original) The composition of claim 1, wherein the amount of the crystal growth inhibitor present in the liquid dosage form ranges from about 0.1% to about 95% concentration, by weight.

9. (Original) The composition of claim 1, wherein the amount of the crystal growth inhibitor present in the liquid dosage form ranges from about 0.5% to about 90% concentration, by weight.

10. (Original) The composition of claim 1, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

11. (Original) The composition of claim 1 or 10, wherein at least about 70%, at least about 90%, or at least about 95% of the active agent particles have a particle size less than the effective average particle size.

12. (Original) The composition of claim 1, wherein the amount of the active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent.

13. (Original) The composition of claim 1, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

14. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

15. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

16. (Original) The composition of claim 1, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

17. (Original) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

18. (Original) The composition of claim 1, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

19. (Original) The composition of claim 1, comprising at least two surface stabilizers.

20. (Original) The composition of claim 19, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

21. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

22. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

23. (Original) The composition of claim 22, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-

D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

24. (Previously Presented) The composition of claim 22, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium

chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

25. (Original) The composition of any of claims 22 or 24, wherein the composition is bioadhesive.

26. (Original) The composition of claim 1, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

27. (Original) The composition of claim 1, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less

than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

28. (Original) The composition of claim 1 wherein the active agent comprises anti-inflammatory and analgesic properties.

29. (Original) The composition of claim 1, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

30. (Original) The composition of claim 29, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin,

glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

31. (Original) The composition of claim 1, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

32. (Previously Presented) The composition of claim 1, having a viscosity, at a shear rate of 0.1 (1/s), is selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from

about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

33. (Previously Presented) The composition of claim 1, having a viscosity selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

34. (Previously Presented) The composition of claim 1, having a viscosity selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

35. (Previously Presented) The composition of claim 1, having a T_{max}, when assayed in the plasma of a mammalian subject following administration, less than the T_{max} for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

36. (Cancelled)

37. (Previously Presented) The composition of claim 1, having a C_{max}, when assayed in the plasma of a mammalian subject following administration, greater than the C_{max} for a

conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

38. (Cancelled)

39. (Previously Presented) The composition of claim 1, having an AUC, when assayed in the plasma of a mammalian subject following administration, greater than the AUC for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

40. (Cancelled)

41. (Original) The composition of claim 1 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

42. (Cancelled)

43. (Original) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is biocquivalent to administration of the composition to a subject in a fed state, when administered to a human.

44. (Original) The composition of claim 43, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

45. (Original) The composition of claim 43, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

46. (Withdrawn) A method of making a stable nanoparticulate liquid dosage composition comprising contacting particles of at least one active agent with at least one surface

stabilizer in the presence of a liquid media for a time and under conditions sufficient to provide a nanoparticulate active agent composition wherein:

(a) the active agent particles have an effective average particle size of less than 2000 nm; and

(b) at least one osmotically active crystal growth inhibitor is added to the composition either before, during, or after the active agent particle size reduction, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt.

47. (Withdrawn) The method of claim 46, wherein said contacting comprising grinding.

48. (Withdrawn) The method of claim 47, wherein said grinding comprising wet grinding.

49. (Withdrawn) The method of claim 46, wherein said contacting comprises homogenizing.

50. (Withdrawn) The method of claim 46, wherein said contacting comprises:

(a) dissolving the particles of at least one active agent in a solvent;

(b) adding the resulting solution of the active agent to a solution comprising at least one surface stabilizer; and

(c) precipitating the solubilized active agent and at least one surface stabilizer by the addition thereto of a non-solvent.

51. (Withdrawn) The method of claim 46, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

52. (Withdrawn) The method of claim 46, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

53. (Cancelled)

54. (Withdrawn) The method of claim 46, wherein the crystal growth inhibitor is glycerol.

55. (Withdrawn) The method of claim 46, where the crystal growth inhibitor is mannitol.

56. (Withdrawn) The method of claim 46, where the crystal growth inhibitor is sodium chloride.

57. (Withdrawn) The method of claim 46, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.1% to about 95% concentration, by weight.

58. (Withdrawn) The method of claim 57, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.5% to about 90% concentration, by weight.

59. (Withdrawn) The method of claim 46, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400

nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

60. (Withdrawn) The method of claim 46 or 59, wherein at least about 70%, about 90%, or about 95% of the active agent particles have a particle size less than the effective average particle size.

61. (Withdrawn) The method of claim 46, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

62. (Withdrawn) The method of claim 46, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

63. (Withdrawn) The method of claim 46, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

64. (Withdrawn) The method of claim 46, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

65. (Withdrawn) The method of claim 46, comprising at least two surface stabilizers.

66. (Withdrawn) The method of claim 65, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

67. (Withdrawn) The method of claim 46, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

68. (Withdrawn) The method of claim 67, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol,

PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

69. (Withdrawn) The method of claim 67, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl

benzencalkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

70. (Withdrawn) The method of claim 46, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

71. (Withdrawn) The method of claim 46, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

72. (Withdrawn) The method of claim 46, wherein the active agent comprises anti-inflammatory and analgesic properties.

73. (Withdrawn) The method of claim 46, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory

agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

74. (Withdrawn) The method of claim 73, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

75. (Withdrawn) The method of claim 46, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine,

felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

76. (Withdrawn) A method of treating a subject with a stable nanoparticulate liquid dosage composition comprising administering to the subject an effective amount of a composition comprising:

(a) particles of at least one active agent having an effective average particle size of less than 2000 nm;

(b) at least one surface stabilizer;

(c) at least one osmotically active crystal growth inhibitor, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt; and

(d) a liquid media.

77. (Withdrawn) The method of claim 76, wherein said subject is a human.

78. (Withdrawn) The method of claim 76, wherein the condition to be treated is selected from the group consisting of neoplastic diseases, breast cancer, endometrial cancer, uterine cancer, cervical cancer, prostate cancer, renal cancer, hormone replacement therapy in post-menopausal women, endometriosis, hirsutism, dysmenorrhea, uterine bleeding, HIV wasting, cancer wasting, migraine headache, cachexia, anorexia, castration, oral contraception,

motion sickness, emesis related to cytotoxic drugs, gastritis, ulcers, dyspepsia, gastroenteritis, including collitis and food poisoning, inflammatory bowel disease, Crohn's disease, migraine headaches, and any other condition which is accompanied by the symptoms of nausea and vomiting.

79. (Withdrawn) The method of claim 76, wherein the condition to be treated is selected from the group consisting of pain, inflammation, arthritis, cancer, kidney disease, osteoporosis, Alzheimer's disease, and familial adenomatous polyposis.

80. (Withdrawn) The method of claim 79, wherein the condition to be treated is selected from the group consisting of osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout, ankylosing spondylitis, systemic lupus erythematosus, bursitis, tendinitis, myofascial pain, carpal tunnel syndrome, fibromyalgia syndrome, infectious arthritis, psoriatic arthritis, reiter's syndrome, and scleroderma.

81. (Withdrawn) The method of claim 76, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

82. (Withdrawn) The method of claim 76, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

83. (Cancelled)

84. (Withdrawn) The method of claim 76, wherein the crystal growth inhibitor is glycerol.

85. (Withdrawn) The method of claim 76, where the crystal growth inhibitor is mannitol.

86. (Withdrawn) The method of claim 76, where the crystal growth inhibitor is sodium chloride.

87. (Withdrawn) The method of claim 76, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.1% to about 95% concentration, by weight.

88. (Withdrawn) The method of claim 76, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.5% to about 90% concentration, by weight.

89. (Withdrawn) The method of claim 76, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

90. (Withdrawn) The method of claim 76 or 89, wherein at least about 70%, about 90%, or about 95% of the active agent particles have a particle size less than the effective average particle size.

91. (Withdrawn) The method of claim 76, wherein the amount of the active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent.

92. (Withdrawn) The method of claim 76, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

93. (Withdrawn) The method of claim 76, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

94. (Withdrawn) The method of claim 76 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

95. (Withdrawn) The method of claim 76, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

96. (Withdrawn) The method of claim 76, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

97. (Withdrawn) The method of claim 76, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

98. (Withdrawn) The method of claim 76, comprising at least two surface stabilizers.

99. (Withdrawn) The method of claim 98, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

100. (Withdrawn) The method of claim 76, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

101. (Withdrawn) The method of claim 76, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

102. (Withdrawn) The method of claim 101, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-

glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

103. (Withdrawn) The method of claim 101, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride

monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

104. (Withdrawn) The method of claim 76, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

105. (Withdrawn) The method of claim 76, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

106. (Withdrawn) The method of claim 76, wherein the active agent comprises anti-inflammatory and analgesic properties.

107. (Withdrawn) The method of claim 76, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins,

peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

108. (Withdrawn) The method of claim 107, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

109. (Withdrawn) The method of claim 76, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin,

cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

110. (Withdrawn) The method of claim 76, wherein the viscosity of the composition, at a shear rate of 0.1 (1/s), is selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

111. (Withdrawn) The method of claim 76, wherein the viscosity of the composition is selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of aetive agent.

112. (Withdrawn) The method of claim 76, wherein the viseosity of the eomposition is seleeted from the group eonsisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viseosity of a standard eonventional non-nanopartieulate liquid dosage eomposition of the same aetive agent at about the same eoneentration per ml of aetive agent.

113. (Withdrawn) The method of elaim 76, wherein the T_{max} of the aetive agent, when assayed in the plasma of a mammalian subjeet following administration, is less than the T_{max} for a eonventional, non-nanopartieulate form of the same aetive agent, administered at the same dosage.

114. (Withdrawn) The method of elaim 113, wherein the T_{max} is seleeted from the group eonsisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the T_{max}, exhibited by a non-nanopartieulate formulation of the same active agent, administered at the same dosage.

115. (Withdrawn) The method of claim 76, wherein the C_{max} of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max}

for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

116. (Withdrawn) The method of claim 115, wherein the C_{max} is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

117. (Withdrawn) The method of claim 76, wherein the AUC of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

118. (Withdrawn) The method of claim 117, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

119. (Withdrawn) The method of claim 76 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

120. (Withdrawn) The method of claim 119, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

121. (Withdrawn) The method of claim 76, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

122. (Withdrawn) The method of claim 121, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

123. (Withdrawn) The method of claim 121, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

APPENDIX B: RELATED PROCEEDINGS

No related proceedings are pending.